




CAPM EVENING EVENT



CANMAT CO-MORBIDITY GUIDELINES



Treating Depression in Specific Medical Conditions

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The Canadian Network for Mood and Anxiety Treatments (CANMAT)

Disclosures

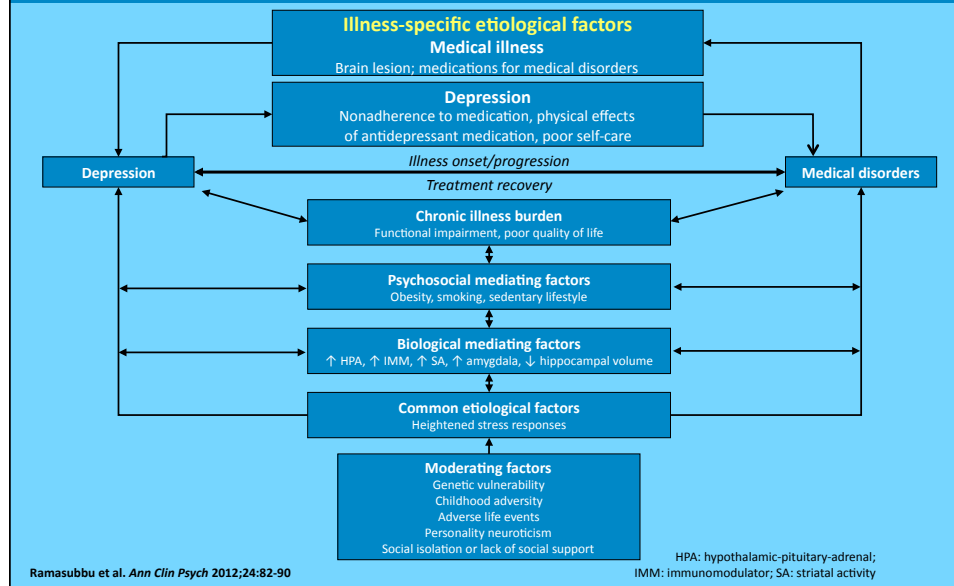
- Co-author on CANMAT co-morbidity guideline in medical populations
- No other conflicts of interest to disclose

Learning Objectives

1. To understand the prevalence of depression in specific medical conditions
2. To identify a treatment approach to depression in medical conditions
3. To analyze the evidence for the pharmacological treatment in medical conditions



Major Depressive Disorder: Interaction with Medical Disorders



Major Depressive Disorder: The Bi-Directional Relationship

MDD: risk factor for development/progression of medical illness

- **Comorbid MDD associated with:**
 - ↑ Medical resource use
 - ↑ Costs
 - ↓ Quality of life
 - Physical symptom amplification
 - Additive functional impairment
- **MDD likely increases medical morbidity through:**
 - Biological mechanisms
 - ↑ HPA axis activity
 - ↑ Sympathetic stimulation
 - ↑ Pro-inflammatory cytokine levels
 - Behaviours
 - Medical treatment non-adherence
 - Self-care neglect
 - Physical inactivity
 - Poor diet
 - Substance use

Major Depressive Disorder: Comorbid Bidirectional Relationship

Medical illness: risk factor for development/progression of MDD

- **Medical conditions likely contribute to development of MDD through:**
 - Direct physiological mechanisms
 - E.g., brain injury and thyroid deficiency
 - Stress-related physiologic mechanisms
 - E.g., increased activation of HPA and immunologic system associated with stress related to physical illness experience or disability
 - HPA axis overdrive and elevated levels of proinflammatory cytokines due to several medical conditions (CVD, stroke, cancer)
 - Psychosocial factors related to illness burden and disability may also contribute to MDD
 - E.g., job loss, financial stress

Ramasubbu et al. *Ann Clin Psych* 2012;24:82-90

CVD: cardiovascular disease;
HPA: hypothalamic-pituitary-adrenal; MDD: major depressive disorder

Major Depressive Disorder: A Risk Factor For the Development of Medical Illness

Medical illness	Comments
Coronary artery disease/ ischemic heart disease	Depression ↑ risk by 1.5-2 fold
Ischemic stroke	Depression ↑ risk by 1.8 fold
Epilepsy	Depression ↑ risk by 4-6 fold
Alzheimer's disease	Depression ↑ risk by 2.1 fold
Diabetes mellitus (type II)	Depression ↑ risk by 60%
Cancer	Depression and life stressors ↑ risk by 1.35-1.88 fold
HIV	Bipolar spectrum conditions may ↑ for HIV infection

Ramasubbu et al. *Ann Clin Psych* 2012;24:82-90

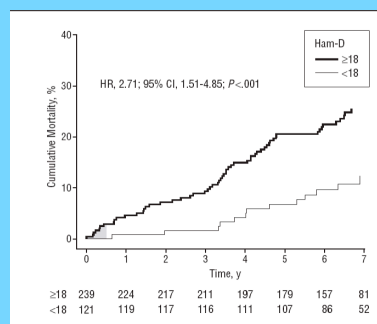
Major Depressive Disorder: A Risk Factor For Poor Medical Outcomes in Patients with Existing Medical Illnesses

Medical illness	Findings
CVD	↑ cardiac mortality 3.5-4 fold & predicts poor prognosis in patients with pre-existing coronary disease
Stroke	↑ mortality 3.4 fold & adversely affects functional recovery
Epilepsy	↑ burden from seizures & decreases quality of life
Diabetes mellitus	↑ earlier onset of vascular complications, functional disability, & death
Cancer	↑ mortality 2.6 fold
HIV	↑ mortality & associated with illness progression to AIDS

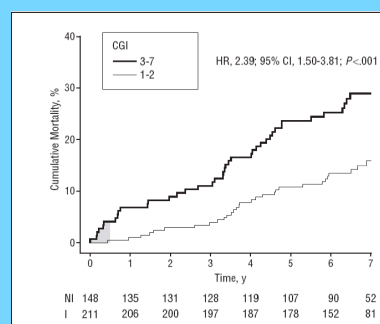
Ramasubbu et al. *Ann Clin Psych* 2012;24:82-90

Long-Term Mortality With CAD and Depression

Glassman AH et al. Arch Gen Psychiatry 2009; 66 (9): 1022-1029



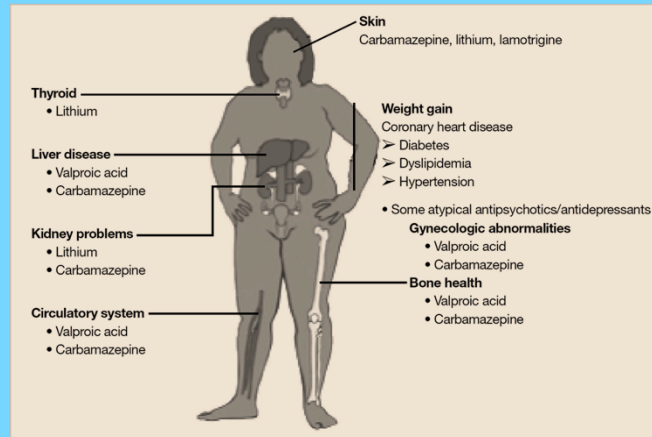
Cumulative mortality based upon severity of depression at baseline



Cumulative mortality by response of depression to sertraline or placebo

Bipolar Disorder/MDD: Contribution of Medication to Comorbidity

Body systems at risk of medication side effects: mood stabilizers



- SSRIs may increase risk of GI and subcutaneous bleeding, linked to osteoporosis
- TCAs may cause orthostatic hypotension, decreased heart-rate variability, QT prolongation

Ramasubbu et al. *Ann Clin Psych* 2012;24:82-90

BD: bipolar disorder; MDD: major depressive disorder

Case Vignette 1: Raymond

Case 1

Background



- 61 y/o, male, civil engineer
- Diagnosed with MDD ~5 years ago
- Initially prescribed sertraline, however he felt the efficacy diminished after ~1.5 years and was switched to fluoxetine
 - Fluoxetine has provided reasonable symptom control and minimal adverse events at maximum recommended dose

Case Vignette 1: Raymond

Case 1



Current visit

- Raymond now presents for a refill of his fluoxetine prescription
- You recall that he suffered a myocardial infarction 6 months ago and is currently taking low-dose ASA
- In addition, he asks you for treatment for his migraines
 - ~3-4/week over the past 2 months

Case Vignette 1: Raymond

Case 1



1. Would you make any changes to Raymond's treatment at this time?

- a) Is his medication the optimal choice for a patient with cardiovascular issues?
- b) Is his medication the optimal choice for a patient with migraines?



Management of Depression in Patients with Medical Comorbidities



- Comprehensive, collaborative treatment involving primary care, medical specialists, nurses, psychologists, social workers
- Treat psychiatric diagnosis as well as related causative factors
- Treatment of some medical conditions may improve comorbid depression
 - E.g., pain, hypothyroidism, vitamin deficiencies

Management of Depression in Patients with Medical Comorbidities Cont.

- Treat depression with antidepressants according to efficacy & safety profile
 - Avoid antidepressants that have negative effects on specific medical illness
 - Consider drug-drug and drug-illness interactions
 - E.g., Certain SSRIs inhibit CYP450 isoenzymes and when used with antiarrhythmics may cause accumulation
 - Imipramine and potential arrhythmic effects in patients because of its antiarrhythmic effect
- Depression in the medically ill may respond poorly, and relapses are common
- Consider psychotherapy, education and case management as appropriate

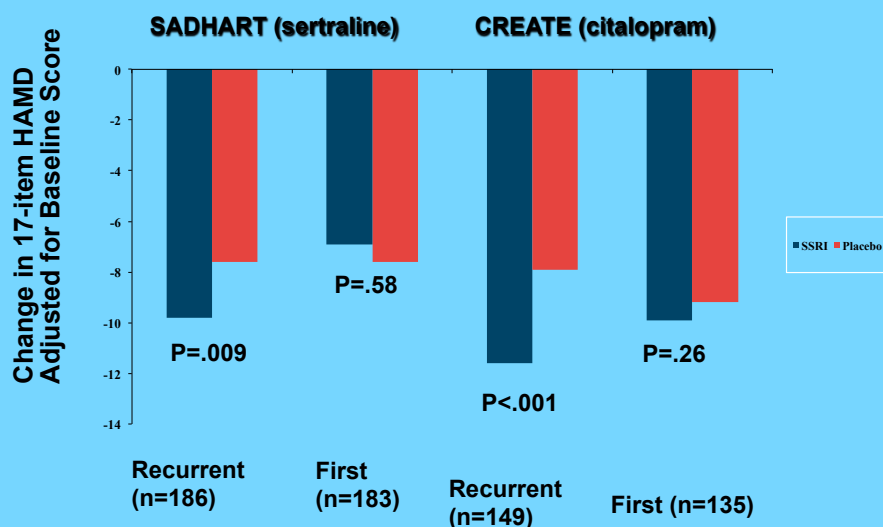
Management of Specific Medical Comorbidities: Cardiovascular Disease

- Routinely screen for depression in patients with CVD in various settings
 - Hospitals, physicians' offices, cardiac rehabilitation centers
- SSRIs and NaSSAs beneficial in treating depression after cardiac event (without worsening of cardiac events)
- Carefully monitor patients with CVD receiving MDD treatment (1st-line evidence)
 - Medical care adherence
 - Drug efficacy
 - Safety (both CV and mental health)
- For mild to moderate depression, psychotherapies (e.g., CBT, IPT, problem-solving therapy) beneficial alone or combined with medication
- No systematic studies evaluating ECT or TMS
 - ECT can be performed safely in most patients with underlying cardiac conditions, but appropriate cardiac treatments should be administered at time of neuromodulation treatment

CBT: cognitive behavioural therapy; CVD: cardiovascular disease; ECT: electroconvulsive therapy; IPT: interpersonal therapy; MDD: major depressive disorder; NaSSA: noradrenergic and specific serotonergic antidepressant; SSRI: selective serotonin reuptake inhibitor; TMS: transcranial magnetic stimulation

Ramasubbu et al. *Ann Clin Psych* 2012;24:91-109

Efficacy of SSRI Treatment for First vs Recurrent Depression in CAD Patients



Management of Specific Medical Comorbidities: Cerebrovascular Disease

FIRST LINE

Citalopram (level 2)
Demonstrated safety in cardiac and elderly patients

SECOND LINE

Nortriptyline (level 1)
Risk of delirium and safety concerns with cardiac patients

THIRD LINE

Amitriptyline, trazodone (level 2); ECT, repetitive TMS,
psychostimulants (level 3, treatment-resistant PSD)

NOT RECOMMENDED

Paroxetine, fluoxetine (level 2)
Interact with cardiac medications

- Use adjunctive antipsychotics with caution for treatment resistant MDD or BD
 - May increase stroke risk in elderly patients
- Routine use of ADs after stroke to prevent depression and improve stroke recovery is not recommended due to lack of adequate evidence
- Structured psychological therapies (e.g., problem-solving therapy, motivational interviewing) + ADs may be beneficial in patients with: (level 4)
 - MDD resistant to 1st-line ADs
 - For relapse prevention

AD: antidepressant; BD: bipolar disorder; CVD: cardiovascular disease;
MDD: major depressive disorder; PSD: post-stroke depression;
TMS: transcranial magnetic stimulation

Ramasubbu et al. *Ann Clin Psych* 2012;24:91-109

Drug Interactions of Common Cardiac Medications

Drug	Metabolism Site	Enzymes Inhibited	Major Interactions
Amiodarone	2C8, 3A4	1A2, 2C9, 2D6, 3A4	Trazodone - QTc prolongation & cases torsades
Warfarin	2C9, 1A2, 2C19	NONE	Potential interaction with fluoxetine and fluvoxamine
Beta-blockers	2D6	2D6 for propranolol	Potential increase concentrations with fluoxetine and paroxetine
Calcium Channel Blockers	3A4		
Diltiazem / Verapamil	3A4	3A4	Could potentiate effects of BZD using 3A4
Ace inhibitors	Unknown	None known	Increase lithium levels

SJ Ferrando et al. 2010

Management of Specific Medical Comorbidities: Cancer

Psychosocial factors that increase risk of depression in cancer patients

- ↑ Attachment anxiety
- ↑ Illness intrusiveness
- Personal or family history of depression
- Maladaptive coping strategies
- ↓ Age
- ↓ Social support
- ↓ Communication with medical caregivers



Ramasubbu et al. *Ann Clin Psych* 2012;24:91-109

Management of Specific Medical Comorbidities: Cancer

Evidence for psychosocial treatment efficacy in preventing/relieving depression

Therapy	Level of evidence
Relaxation techniques	
Newly diagnosed patients	1
Undergoing surgery	1
Undergoing chemotherapy	1
Undergoing radiotherapy	1
Completion of active treatment	2
Terminal phase of illness	2
Psychoeducation	
Newly diagnosed patients	2
Undergoing surgery	2
Undergoing chemotherapy	2
Supportive-expressive therapies	
Undergoing surgery	2
Undergoing chemotherapy	2
Undergoing radiotherapy	2
Patients with metastatic disease	1
Cognitive-behavioural therapies	
Undergoing chemotherapy	1
Patients with metastatic disease	1

Evidence for pharmacotherapy efficacy in preventing/relieving depression

Agent	Level of evidence
Antidepressants	
Paroxetine	1
Fluoxetine	2
Citalopram	2
Mianserin	1
Desipramine	No evidence
Amitriptyline	No evidence
Mirtazapine	3
Bupropion	3
Anxiolytics	
Alprazolam	2
Steroids	
Prednisone	2
Stimulants	
Methylphenidate	3
Mazindol	No evidence

Ramasubbu et al. *Ann Clin Psych* 2012;24:91-109

Management of Specific Medical Comorbidities: Cancer

Treatment recommendations

Limited evidence on which to base 1st-line treatment recommendations

- Level 1 evidence available only for paroxetine in depression prevention trials
 - However, caution recommended based on strong inhibition of cytochrome P450 2D6 and anticholinergic side effects
- Currently no evidence any particular AD more efficacious than another

1st-line treatment recommendations for specific psychosocial interventions

- Therapies shown to be helpful, but evidence does not support superiority of one modality over another
- Patient characteristics guide choice

Ramasubbu et al. *Ann Clin Psych* 2012;24:91-109

Bi-Directional Effects of HIV and Depression HIV

- Depression is considered a vector for HIV transmission through high risk behaviours
- Depression can influence HIV immune activity and course of infection:
 - NK cell numbers & functioning
 - Increase in activated CD8 lymphocytes
 - Increased viral load
- Stigma of HIV and potential interpersonal losses can precipitate depression
- Efavirenz (HAART) can cause depression in ~20% of patients

Alciati A et al. *Psychopharmacol* 2007; Evans DL et al. *Am J Psychiatry* 2002; Lochet P et al. *HIV Med* 2003; Treisman G et al. *Depress Anxiety* 1998

Management of Specific Medical Comorbidities: HIV

- **SSRIs recommended due to good tolerability profile in treating depression in HIV-positive patients (level 1)**
 - Fluoxetine, paroxetine, sertraline, citalopram, escitalopram
 - Escitalopram or citalopram may be preferred due to limited drug-drug interactions with highly active antiretroviral therapy (HAART) (level 1)
- **TCAs should be used only after failure of SSRIs (level 2)**
 - Discontinuation potential due to adverse effects
- **Stimulants may be effective (level 2)**
 - E.g., dextroamphetamine, methylphenidate
- **Psychosocial therapies (level 2)**
 - Evidence exists for use of a range of interventions (e.g., CBT, supportive psychotherapy, psychoeducational groups, IPT)

Ramasubbu et al. *Ann Clin Psych* 2012;24:91-109

CBT: cognitive behavioural therapy; IFN: interferon- α -induced;
IPT: interpersonal therapy; MDD: major depressive disorder;
SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

Management of Specific Medical Comorbidities: HCV

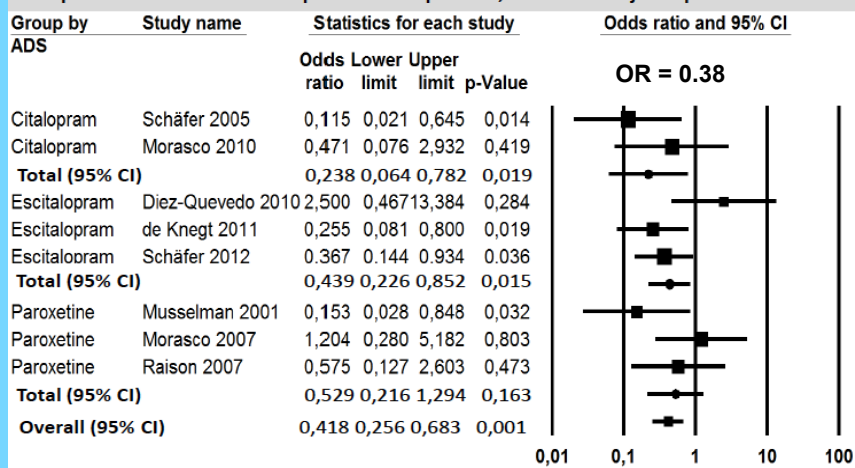
- Now have 1st line treatment for depression HCV- or IFN-MDD – escitalopram (level 1)
- Citalopram (level 2) and escitalopram (Level 1) show significant effect and good tolerability in patients with HCV
- Some evidence of benefit with fluoxetine, sertraline, venlafaxine, bupropion, mirtazapine, nortriptyline, and imipramine use for IFN-MDD (level 3)
- Prophylactic paroxetine failed but escitalopram shown to reduce incidence of IFN-MDD (level 1)
- Amantadine failed to demonstrate significant effect in IFN-MDD and had poor tolerability (level 2)
- Limited research for psychosocial interventions, alone or in combination with pharmacotherapy (level 3)

Ramasubbu et al. *Ann Clin Psych* 2012;24:91-109
Sarker S et al. *Psychosomatics* 2013

CBT: cognitive behavioural therapy; IFN: interferon- α -induced;
IPT: interpersonal therapy; MDD: major depressive disorder;
SSRI: selective serotonin reuptake inhibitor; TCA: tricyclic antidepressant

New Data on Antidepressant Pre-Treatment in Patients Undergoing Hepatitis C Treatment with IFN α

Comparison of different antidepressants vs. placebo; outcome: major depression



Three Antidepressants Used: Citalopram, Escitalopram, Paroxetine

Sarker S et al. *Psychosomatics* 2013;

Management of Specific Medical Comorbidities: Migraine

- Patients with MDD should be screened for migraine using standardized tools
- Combination therapy recommended to control migraine symptoms (level 1)
 - May include anticonvulsants (e.g., valproate, β -blockers, calcium channel-blockers)
- Amitriptyline and SNRIs have shown significant prophylactic effect on migraine (level 1)
- SSRIs have also shown prophylactic efficacy in migraine (level 2 and 3), however some may exacerbate migraine
- Psychotherapeutic approaches have a role in both MDD and migraine (level 3)
 - E.g., patient education, CBT, biofeedback
- Somatic treatments have shown promise (e.g., TMS or VNS) (level 3)

Ramasubbu et al. *Ann Clin Psych* 2012;24:91-109

CBT: cognitive behavioural therapy; MDD: major depressive disorder;
SNRI: serotonin-norepinephrine reuptake inhibitor; SSRI: selective serotonin reuptake inhibitor;
TMS: transcranial magnetic stimulation; VNS: vagus nerve stimulation

Management of Specific Medical Comorbidities: Migraine

Evidence for migraine prophylactic treatment

Agent (level of evidence)	Comments	Agent (level of evidence)	Comments
Antidepressants		Antiepileptics	
Amitriptyline (1)	Most commonly used	Topiramate (1)	May worsen depression
Venlafaxine (1)	-	Valproate (1)	1 st -line migraine prophylaxis
Citalopram (2)	Tested in patients with migraine and depression	Gabapentin (2)	-
Escitalopram (2)	Tested in migraine without depression	Lamotrigine (3)	-
Fluoxetine (2)	May worsen headache		
Sertraline (3)	May worsen headache	Beta-blockers	
Paroxetine (3)	May worsen headache	Propranolol (1)	-
Bupropion (3)	-		
Mirtazapine (3)	Individual case reports	CCBs	
Duloxetine (3)	-	Verapamil (2)	-

Ramasubbu et al. *Ann Clin Psych* 2012;24:91-109

Management of Specific Medical Comorbidities: Epilepsy

First step in effective treatment of comorbid depression in patients with epilepsy is control of seizures with anti-epileptics

FIRST LINE	None
SECOND LINE	Citalopram, escitalopram, sertraline, lamotrigine monotherapy or add-on (for unipolar depression)
THIRD LINE	Venlafaxine
NOT RECOMMENDED	<ul style="list-style-type: none"> Anticonvulsants with potential depressogenic properties or increased suicidal risk (e.g., phenobarbitone, primidone, tiagabine, vigabatrin, felbamate, topiramate)* ADs with strong proconvulsive properties (e.g., bupropion, maprotiline, amoxapine) TCAs (consider only in treatment-resistant MDD) Avoid AD polypharmacy, higher AD doses, rapid titration

*If these produce best seizure control, depressive episodes triggered by these medications can be symptomatically treated with ADs

AD: antidepressant; MDD: major depressive disorder;
TCA: tricyclic antidepressant;

Ramasubbu et al. *Ann Clin Psych* 2012;24:91-109

Management of Specific Medical Comorbidities: Osteoporosis

- Routine bone mineral density (BMD) screening via dual-energy X-ray absorptiometry (DEXA) recommended for:
 - Patients >40 y with long-term SSRI exposure (<2 yrs) (level 2)
 - Patients receiving mood stabilizers as long-term therapy (level 1)
- Vitamin D₃ supplementation recommended in patients >50 y at moderate risk of vitamin D deficiency (800-1000 IU/d [20-25 mcg]) (level 2)

Ramasubbu et al. *Ann Clin Psych* 2012;24:91-109

SSRI: selective serotonin reuptake inhibitor

Management of Patients with Comorbid Medical Conditions: Summary



- MDD treatment in patients with comorbid medical issues should be comprehensive and collaborative
 - Include primary care, medical specialists, nurses, psychologists, social workers
- Once MDD diagnosis established, treatment should focus on both MDD and related causative factors
 - Treat MDD with antidepressants and psychotherapy according to current guidelines
- Psychotherapy, education, and case management should be considered as appropriate

MDD: major depressive disorder

Management of Patients with Comorbid Medical & Mood Disorders: Summary



- Mood disorders are highly co-morbid with major medical disorders
- Co-morbid depression significantly impacts disability, morbidity and mortality in medically ill patients
- Screening for depression is key as depression can be under-diagnosed in the medically ill
- Evidence-based options for treating depression in the medically ill are increasing...
- Further studies are needed in this patient population, specifically focusing on treatment and common pathoetiological pathways